

Slimming to the Death: Herbalife®-Associated Fatal Acute Liver Failure—Heavy Metals, Toxic Compounds, Bacterial Contaminants and Psychotropic Agents in Products Sold in India



Cyriac A. Philips *, Philip Augustine *, Sasidharan Rajesh *, Solomon K. John *,
Gopakumar C. Valiathan *, Jos Mathew *, Sameer Phalke †, Kuruveetil L. Antony ‡

**The Liver Unit, The Cochin Gastroenterology Group, Ernakulam Medical Centre, Kochi, Kerala 682028 India, †Medgenome Labs, Narayana Health City, Bommasandra, Bengaluru, Karnataka 560099 India and ‡Envirotechnologies Ecolabs, Eco Tower, Palarivattom, Kochi, Kerala 682025 India*

Herbalife® is a global nutrition and weight management company selling and marketing nutritional and weight loss supplements. The United States Federal Trade Commission described Herbalife® in 2016 as a scam disguised as healthy living. Herbalife®-associated liver injury was reported from multiple countries in the West. India is fast becoming the largest growing market for Herbalife® products, expected to surpass the United States in sales revenue. We report the first case of a fatal acute liver failure from the Asia-Pacific region, in a young woman who consumed Herbalife® products over 2 months. We also present unsettling data that showcase heavy metal contamination, toxic compounds, psychotropic substances, and pathogenic bacterial contamination in similar Herbalife® products in India. The growth of Herbalife® in India and expansion of its nutrition clubs in major cities that promise fake health benefits portend a serious public health concern. (J CLIN EXP HEPATOLOGY 2019;9:268–272)

Herbal and dietary supplements (HDSs) are increasingly used among the general population and remain a growing market globally. They can be procured without prescription and are generally consumed without specific medical advice and monitoring. Unlike standard prescription drugs, the safety and efficacy of HDSs are not well studied. The marketing of HDSs as food supplements surpass required preclinical and clinical testing in many countries. Well-described large studies have shown that various HDSs are associated with severe liver injury.¹ Herbalife® is a global nutrition, weight management and direct selling company that develops, markets and sells nutritional and weight loss supplements, sports nutrition and personal care products. Herbalife®-associated liver injury was initially reported from Israel, fol-

lowed by Spain, Switzerland, Iceland, Argentina and the United States.² Recently, India has become the largest growing market for Herbalife® products and is expected to surpass United States in sales revenue in the coming years. We report the first case of Herbalife®-associated fatal acute liver failure from the Asia-Pacific region in a young woman who consumed three products over a period of 2 months. We also present unsettling data of comprehensive chemical analysis, toxicology and microbial contamination studies of similar Herbalife® products retrieved from the patient's original place of purchase (a nutritional club at Kottakkal in Kerala) and those purchased online from different regions in India.

CASE REPORT

A 24-year-old woman with hypothyroidism without other chronic illnesses, on thyroxine supplementation in the last 5 years (75mcg once daily), with a body mass index of 32.1 was initiated on three Herbalife® slimming products (Formula 1 Shake Mix, two scoops twice daily with skimmed milk; Personalized Protein Powder, two tablespoons into the Shake Mix twice daily and Afresh Energy Drink, 10 g twice daily), purchased from a local nutrition club. The patient was not on any other medications or complementary and alternative drugs before or during this time. After 2

Keywords: Herbal supplements, HILI, obesity, weight loss, liver disease
Received: 18.5.2018; **Accepted:** 16.8.2018; **Available online:** 28 August 2018

Address for correspondence: Cyriac Abby Philips MD DM, Philip Augustine Associates, 35/194 B, Symphony, Automobile Rd, Palarivattom, Kochi, Kerala 682025 India. Tel.: +91 9207745776.

E-mail: abbyphilips@gmail.com

Abbreviations: AIH: Autoimmune Hepatitis; BL: Butyrolactones; HDSs: Herbal and Dietary Supplements; ULN: Upper Limit of Normal
<https://doi.org/10.1016/j.jceh.2018.08.002>

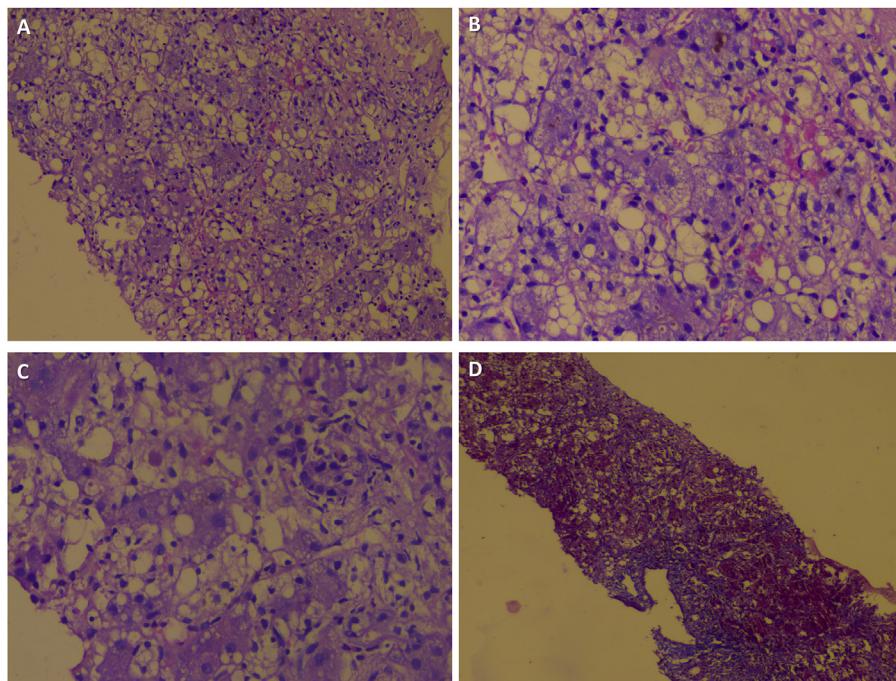


Figure 1 Liver biopsy showing (A) distorted hepatic architecture with severe steatosis with balloon degeneration, mixed lymphocytic and neutrophilic inflammation; (B) interface hepatitis along with intracanalicular cholestasis; (C) cholangitis (haematoxylin and eosin stain, 20 \times) and (D) periportal and perivenular bridging necrosis (Masson trichrome stain, 20 \times).

months, she developed progressive loss of appetite for a week, followed by jaundice and transient pruritus. Initial blood work revealed that total serum bilirubin level was 12.4 (upper limit of normal [ULN] 1.1 mg/dL); direct bilirubin, 9.9 (ULN 0.2 mg/dL); aspartate aminotransferase, 582 (ULN 36 U/L); alanine aminotransferase, 648 (ULN 45 U/L); alkaline phosphatase, 248 (ULN 120 U/L); gamma-glutamyl transferase level, 398 (ULN 35 U/L); albumin, 3 (ULN 5.5 g/dL) and international normalised ratio, 4.7 (normal < 1.2). Twelve days later, jaundice worsened (total bilirubin 28.6 mg/dL), and she was brought to our emergency in grade 3 hepatic encephalopathy. Blood investigations for acute and chronic viral hepatitis including herpes simplex and zoster virus, cytomegalovirus, parvovirus, human immunodeficiency virus and human T-cell lymphotropic virus and autoimmune hepatitis (antinuclear antibody, anti-liver kidney muscle antibody type 1, anti-smooth muscle antibody) were negative. The serum gamma globulins were raised (2682 mg/dL, normal 620–1400). The simplified autoimmune hepatitis (AIH) score was 4 (score <6 unlikely to be AIH). Serum ceruloplasmin and iron studies were normal. An ultrasound imaging of the abdomen revealed fatty hepatomegaly with normal biliary and vascular anatomy without evidence of portal hypertension. Drug-induced liver injury secondary to Herbalife® supplement was considered, with Roussel Uclaf Causality Assessment Method score 6 (probable adverse reaction). A transjugular liver biopsy showed exten-

sive periportal and perivenular bridging necrosis with moderate-to-severe mixed inflammatory infiltration, interface hepatitis, cholangitis, severe ballooning, steatosis and intracanalicular cholestasis (Figure 1). With fulfilment of King's College criteria, the patient was urgently referred to a transplant centre, but she passed away on wait list soon after. It was difficult for us to retrieve the Herbalife® samples from the bereaving family. However, we were able to source one product from the same seller from where the patient had initially made the purchase. This nutritional club was functioning without a licence, selling Herbalife® products in the name of health and wellness and was eventually shutdown by the Department of Health Services, Government of Kerala. We also sourced similar Herbalife® products from the internet (total of 8 samples) and subjected them to heavy metal analysis (inductively coupled plasma optical emission spectrometry [Agilent Technologies, Santa Clara, California, USA]) and toxicology (triple quadrupole gas chromatography and dual mass spectroscopy [Thermo Fisher Scientific, Waltham, Massachusetts, USA]) and bacterial contamination studies using 16S RNA metagenomics (Illumina MiSeq next-generation sequencer [Illumina, California, USA]; operational units classified taxonomically according to the Greengenes Database; Shannon diversity index for description of species diversity in each bacterial community using the Quantitative Insights Into Microbial Ecology). The details of chemical analysis and toxicology are shown in Table 1. We found

Table 1 Disclosed Components, Chemical Analysis and Toxicology of Herbalife® Products Sourced From the Internet.

S no	Product name	Area of origin	Chemical analysis: element ^a (mg/kg)	Toxicology ^b (qualitative); undisclosed
1	Afresh drink	Kottakal, Kerala (patients' purchase origin)	Ba (3.4), Cr (3.9) Pb (2), Th (1.9), Hg (3)	Hydroxy acetic acid Propenoic acid
2	Personalized protein powder	Thane, Maharashtra	Cd (0.19), Ba (4.75), Cr (2.33), Pb (1.55), Th (1.65)	–
3	Afresh drink	Thane, Maharashtra	Ba (2.84), Cr (6.1) Pb (3.1), Th (2.4)	Cyclopropene
4	Formula 1 shake	Thane, Maharashtra	Ba (3.5), Cr (1.5), V (3.5), Th (26.24)	Butyrolactone, Glucosamine
5	Personalized protein powder	Kolkata, West Bengal	Ba (5.1), Cr (7.4)	–
6	Personalized protein powder	Gurugram, Haryana	Cr (7), Th (11.96)	Propene, Hydrazine
7	Afresh drink	New Delhi, Delhi	Cd (3.5), Ba (2.4), Cr (3)	Cyclopropene, Hydrazine
8	Afresh drink	Hisar, Haryana	Cd (3), Cr (3.2), V (6), Th (2.9)	Butyrolactone
Herbalife® products		Disclosed product components	Suspected toxic components in literature	
Afresh drink	Maltodextrin, green tea extracts, guarana seed extract, citric acid, caffeine powder, flavouring substances	Solidaginis gigantea, Ilex paraguariensis, Petroselinum crispum, Garcinia cambogia, Spiraea, Matricaria chamomilla, Liquiritia, Foeniculum amare, Humulus lupulus, Cr		
Personalized protein powder	Soy protein isolate, whey protein concentrate, natural flavour, silicon dioxide, milk, soy			
Formula 1 shake	Soy protein, fructose, cellulose powder, corn bran, guar gum, minerals, rice fibre, soy lecithin, canola oil, carrageenan, medium chain triglycerides, citrus pectin, psyllium husk powder, ginger root powder, proteases of <i>Aspergillus</i> , honey powder, ascorbic acid, dl-alpha tocopherol, papaya fruit, carotene, pantothenate, bromelain, papain powder, folic acid, pyridoxine, thiamine, riboflavin, cholecalciferol, cyanocobalamin			

^aBa, Barium; Cr, Chromium; Pb, Lead; Th, Thallium; Hg, Mercury; V, Vanadium; Cd, Cadmium.

^bUndisclosed.

high levels of heavy metals in all the sourced Herbalife® products and undisclosed toxic compounds including traces of psychotropic recreational agent in 75% of samples. On microbial analysis, bacterial deoxyribonucleic acid was isolated from 63% of samples. 16s RNA analysis revealed multiple bacterial communities, including highly pathogenic species (Figure 2), in Herbalife® products.

DISCUSSION

Zambrone et al performed a literature search to study Herbalife®-related hepatotoxicity (January 2000–February 2015) and found 32 publications, seven of which were reports describing total 53 cases.³ Herbalife® products have been shown to produce hepatocellular, cholestatic and mixed type (seen in our patient) of liver injury. The first series (12 patients) by Elinav et al from Israel described predisposition to Herbalife® toxicity in the presence of underlying liver disease and strong association of Herbalife®-associated liver injury with re-exposure in three patients.⁴

Schoepfer et al described 10 cases of hepatotoxicity potentially involving Herbalife® products in the absence of comorbidity. All patients consumed at least 3 products at the same time, complicating the search for a specific hepatotoxin.⁵ In both instances, the efforts by the authors to recover a detailed product composition of implicated Herbalife® products were apparently unsuccessful as the company declined to provide such information. Stickel et al in 2009 performed toxicology, immunological sensitivity tests and microbiological contamination of Herbalife® products potentially related to liver injury. No significant contamination with heavy metals or pesticides was identified, but contamination with *Bacillus subtilis* with the potential for dose-dependent liver injury was identified.⁶ In our analysis, we found high levels of multiple heavy metals in 75% of samples, a finding contrasting with Western literature and with potential to produce cumulative and severe hepatotoxicity.⁷ We detected pathogenic bacterial phyla (Proteobacteria and Cyanobacteria) with the potential to cause liver injury in 63% of

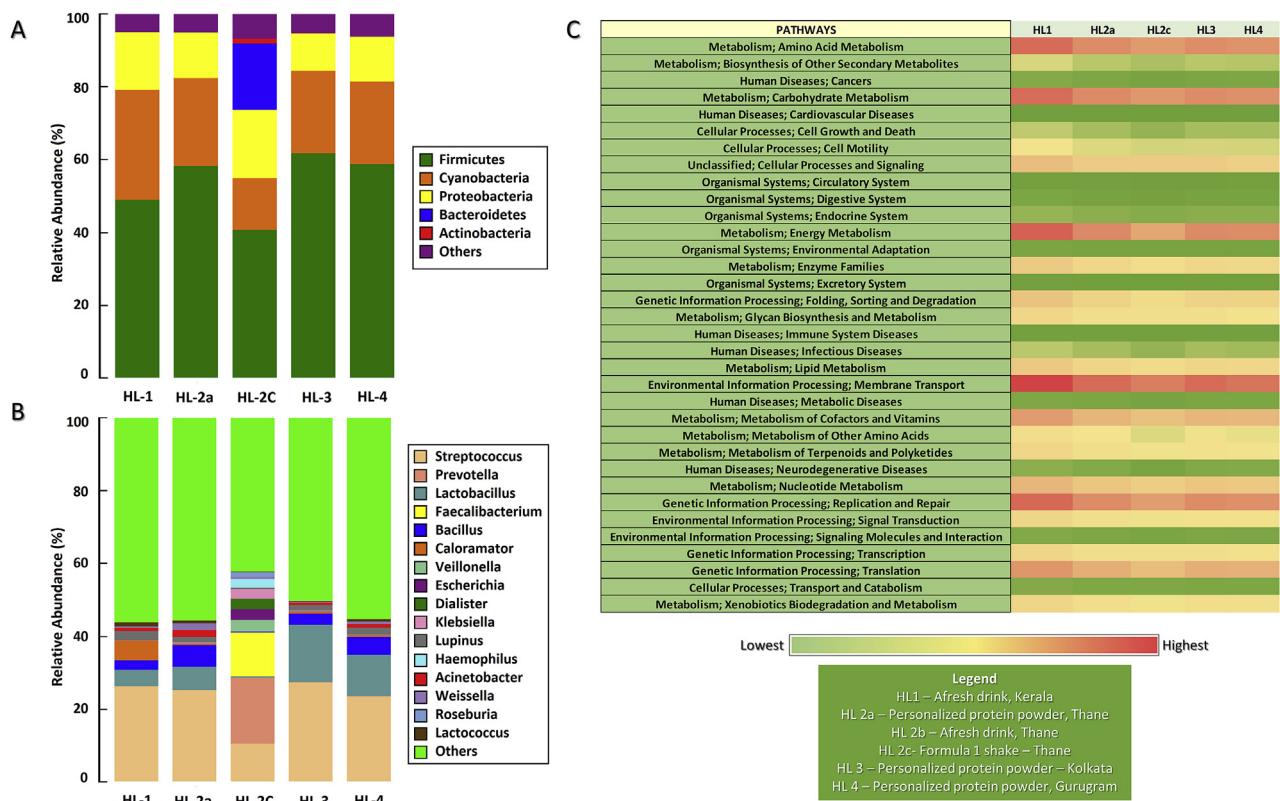


Figure 2 16S RNA metagenomic analysis of the sourced Herbalife® samples showing (A) top 5% of significantly detected bacterial families (relative abundance); (B) bacterial genera that include pathogenic species and (C) the microbiota in the sourced samples predominantly expressed putative metabolic functional pathways associated with energy and amino acid metabolism and human diseases and infections.

samples analysed, which include perilous genera such as *Escherichia*, *Klebsiella*, *Acinetobacter* and *Streptococcus*. This level of microbial detection is unacceptable in processed/vacuum packed food supplements according to the current Good Manufacturing Practices rules and regulations and portends a public health threat that could lead to severe organ damage with repeated and long-term use. We also found other potential liver toxic agents such as glucosamine and hydrazine.^{8,9} The high immunoglobulin levels noted in our patient could have represented seronegative AIH. However, the simplified AIH score showed the diagnosis to be unlikely, and the presence of high immunoglobulin levels with or without autoantibodies is well described in herbal medicine-associated drug induced liver injury (DILI).^{10,11} The presence of butyrolactones (BL) in a quarter of samples tested in our study is of great concern. Gamma-hydroxybutyrate and its precursors are recreational drugs of abuse. The United Nations Expert Committee on Drug Dependence stated that BL be used only for chemical industrial purposes and placed it under the Controlled Substances Act, while the US Food and Drug Administration warned on its use in food substances.^{12–14} The estimated incidence of liver toxicity is 25–30 cases per 100,000 consumers of Herbalife® products.¹⁵ Other

possible explanations for Herbalife®-associated liver injury include microbial spoilage and chemical contamination due to production heterogeneity. No further cases have been observed after the latest series in 2015 until now. Even though we could not analyse the exact Herbalife® products consumed by the patient, we were able to demonstrate toxins in products sourced from the same seller and in similar products sold in India. We also believe that it is not only the heavy metals but also possible unknown but toxic phytochemical constituents and adulterants that would have aggravated the liver injury in our patient. In an important editorial, speculations of why cases of Herbalife hepatotoxicity were only noticed in Europe, Israel and Americas was questioned, even though these products were sold in >90 countries at the time. Our report, the first from Asia-Pacific probably, clears that confusion as potential Herbalife® toxicity is evident from an increased use of Herbalife® products in a region that is sufficiently powered to identify and report it. Other high consumption regions such as Vietnam and Cambodia maybe under reporting the adverse events associated with a ‘safe food supplement’. Herbal nutritional supplements have uncharacterised, unlabelled, inconsistent and mostly undisclosed components without clear health (probably most often harmful) benefits. Many nutritional companies

advertise that health advantages could be seen with long-term repeated use of their nutritional supplements (that are quite expensive) without clinical evidence for the same. Even practicing physicians many of whom lack knowledge about HDSs are often led astray by company executives who market such products as safe or add on nutritional agents. For the layman, advertisement and word of mouth is 'scientific evidence', the fire to which 'social media' and 'franchisees' add fuel to. These advertisements cater to raise false hopes and expectations towards improving a difficult lifestyle change, for example, weight loss, cure from diabetes, control of dyslipidaemia and so forth, with strong clinical or scientific evidence. As with any drug, it is important to put HDSs through preclinical and clinical scientific studies and postmarketing vigilance so that unknown and potentially harmful causes for severe adverse effects, such as liver failure due to the use of such agents, may be more identifiable and controlled. With increase in growth of herbal and dietary nutritional supplement use and expansion of associated nutrition clubs in India and with adequate evidence of liver toxicity and presence of unfavourable substances in such products, there is without doubt a growing public health concern in our hands.

CONFLICTS OF INTEREST AND FINANCIAL DISCLOSURE

The authors have none to declare.

REFERENCES

1. Navarro V, Khan I, Björnsson E, Seeff LB, Serrano J, Hoofnagle JH. Liver injury from herbal and dietary supplements. *Hepatology*. 2017;65:363–373.
2. Teschke R, Frenzel C, Schulze J, Schwarzenboeck A, Eickhoff A. Herbalife® hepatotoxicity: evaluation of cases with positive reexposure tests. *World J Hepatol*. 2013;5:353–363.
3. Zambrone FAD, Corrêa CL, Amaral LMS. A critical analysis of the hepatotoxicity cases described in the literature related to Herbalife® products. *Braz J Pharm Sci*. 2015;51:785–796.
4. Elinav E, Pinsker G, Safadi R, et al. Association between consumption of Herbalife® nutritional supplements and acute hepatotoxicity. *J Hepatol*. 2007;47:514–520.
5. Schoepfer AM, Engel A, Fattinger K, et al. Herbal does not mean innocuous: ten cases of severe hepatotoxicity associated with dietary supplements from Herbalife products. *J Hepatol*. 2007;47:521–526.
6. Stickel F, Droz S, Patsenker E, Bögli-Stuber K, Aebi B, Leib SL. Severe hepatotoxicity following ingestion of Herbalife nutritional supplements contaminated with *Bacillus subtilis*. *J Hepatol*. 2009;50:111–117.
7. Jaishankar M, Tseten T, Anbalagan N, Mathew BB, Beeregowda KN. Toxicity, mechanism and health effects of some heavy metals. *Interdiscipl Toxicol*. 2014;7:60–72.
8. Cerda C, Bruguera M, Parés A. Hepatotoxicity associated with glucosamine and chondroitin sulfate in patients with chronic liver disease. *World J Gastroenterol*. 2013;19:5381–5384.
9. Hussain SM, Frazier JM. Cellular toxicity of hydrazine in primary rat hepatocytes. *Toxicol Sci*. 2002;69:424–432.
10. Sebode M, Schulz L, Lohse AW. "Autoimmune-Like" drug and herb induced liver injury: new insights into molecular pathogenesis. *Int J Mol Sci*. 2017;18:1954.
11. Philips CA, Paramaguru R, Joy AK, Antony KL, Augustine P. Clinical outcomes, histopathological patterns, and chemical analysis of Ayurveda and herbal medicine associated with severe liver injury—A single-center experience from southern India. *Indian J Gastroenterol*. 2018;37:9–17.
12. Schep LJ, Knudsen K, Slaughter RJ, Vale JA, Mégarbane B. The clinical toxicology of γ -hydroxybutyrate, γ -butyrolactone and 1,4-butanediol. *Clin Toxicol*. 2012;50:458–470.
13. https://www.unodc.org/documents/commissions/CND/CND_Sessions/CND_58/ECN72015_8_eV1501009.pdf.
14. Institute of Medicine (US) and National Research Council (US). *Committee on the Framework for Evaluating the Safety of Dietary Supplements. Proposed Framework for Evaluating the Safety of Dietary Supplements: For Comment*. Washington (DC): National Academies Press (US); 2002. Appendix D, Table of Food and Drug Administration Actions on Dietary Supplements. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK220875/>.
15. Shouval D, Elinav E. Herbalife revisited: reply. *J Hepatol*. 2008;49:293–294.